Issues in Radiation-related Breast Cancer Risk

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Overview of Radiation-Related Breast Cancer Risk

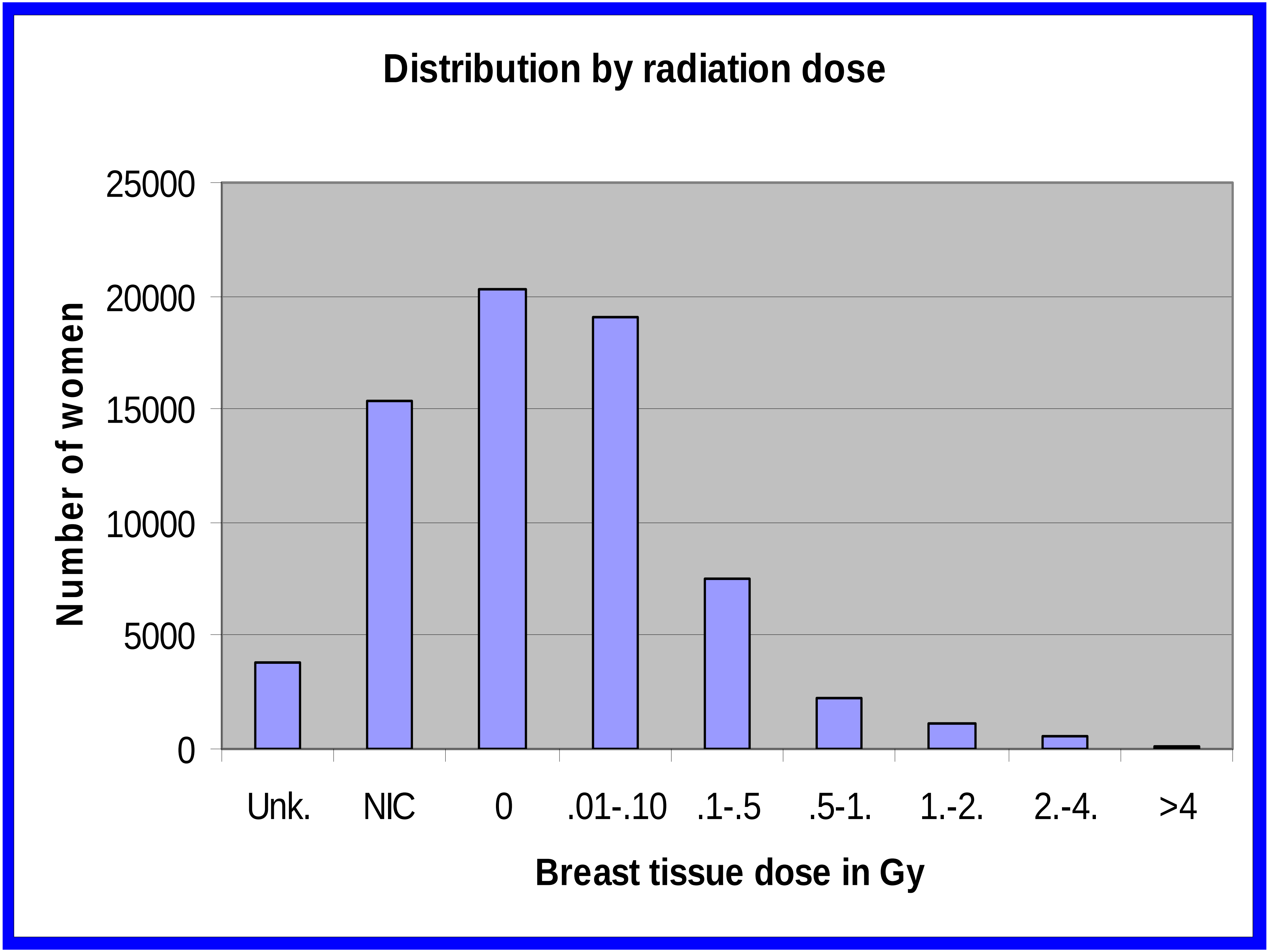
- Demonstrated in different irradiated populations
  - TB fluoroscopy patients
  - A-bomb survivors
  - Benign breast disease
  - Infants with “enlarged thymus”
  - Scoliosis patients
  - Radium dial painters
  - Hemangioma patients
  - Hodgkin disease patients
  - Mayak plutonium workers

Issues

- Dose response – risk per unit dose
  - Extrapolation of risk to low doses & dose rates
  - Radiation quality (gamma ray cf. medical x ray)
- Dose-response modifiers
  - Age at exposure
  - Age at diagnosis (attained age)
  - Reproductive history
  - Secular changes in baseline risk within populations
  - Population baseline risk: how do we transfer risk estimates to other populations?

The RERF Life Span Study

- Cohort of 94,000 A-bomb survivors and 26,000 non-exposed comparison subjects
- Initial selection based on addendum to 1950 Japanese national census
  - Survivors resident in Hiroshima or Nagasaki on October 1, 1950, 5 years after the bombings
- Individual dose estimates (92% of survivors)
  - Interviews, location ATB, detailed shielding histories
  - Neutron-weighted dose, in Sv (neutron wt. = 10)


Distribution by radiation dose
Number of women
25000
20000
15000
10000
5000
0
Unk.
NIC
0
.01-.10
.1-.5
.5-1.
1.-2.
2.-4.
>4
Breast tissue dose in Gy

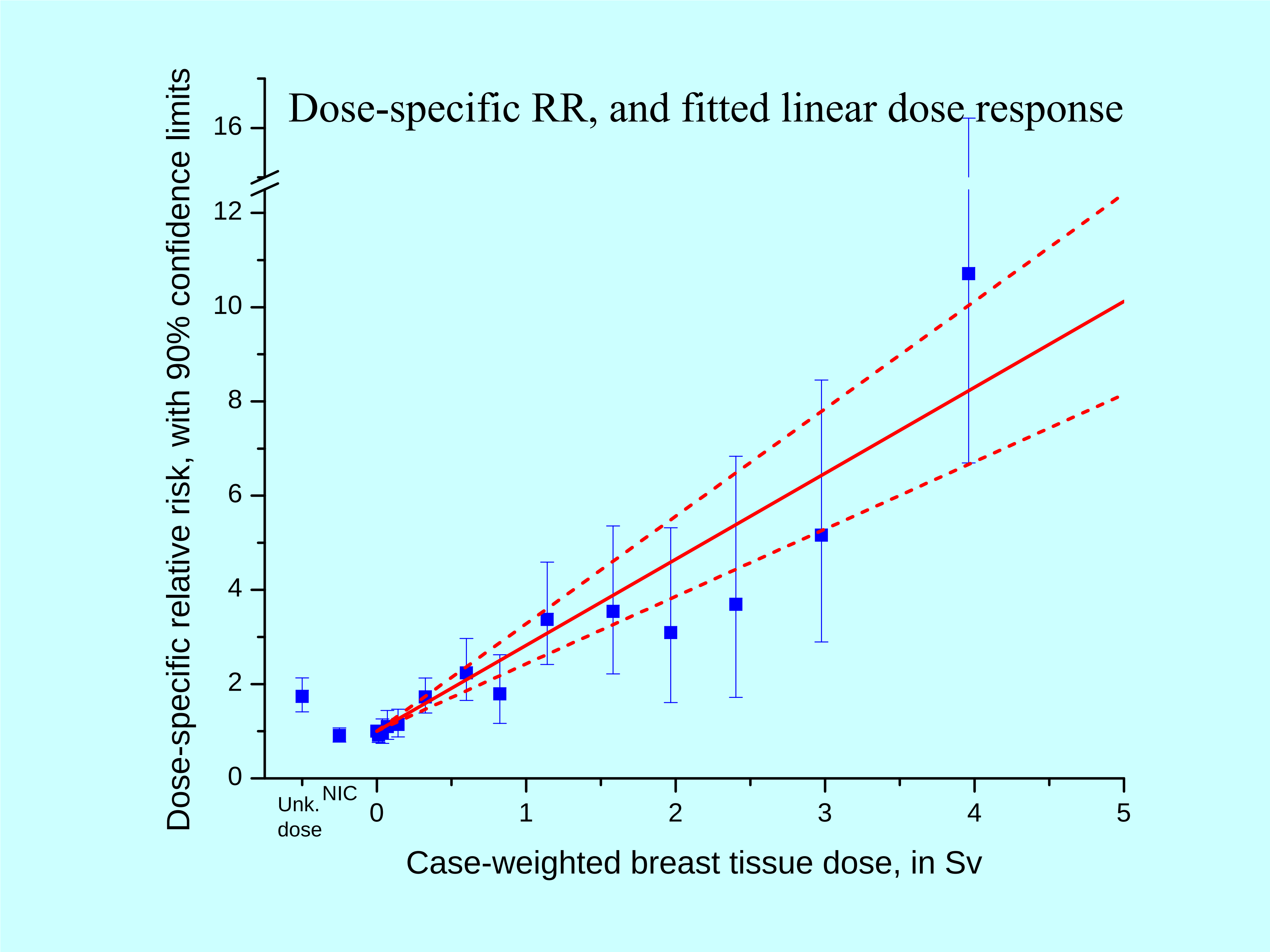
LSS Study: Resources

- Complete mortality follow-up at level of death certificate dx
- Tumor registry, based on local Hiroshima and Nagasaki registries, established 1958
- Tissue registry
- Clinical subsample
  - Examined on 2-year cycle
  - Stored serum, lymphocytes, clinical records

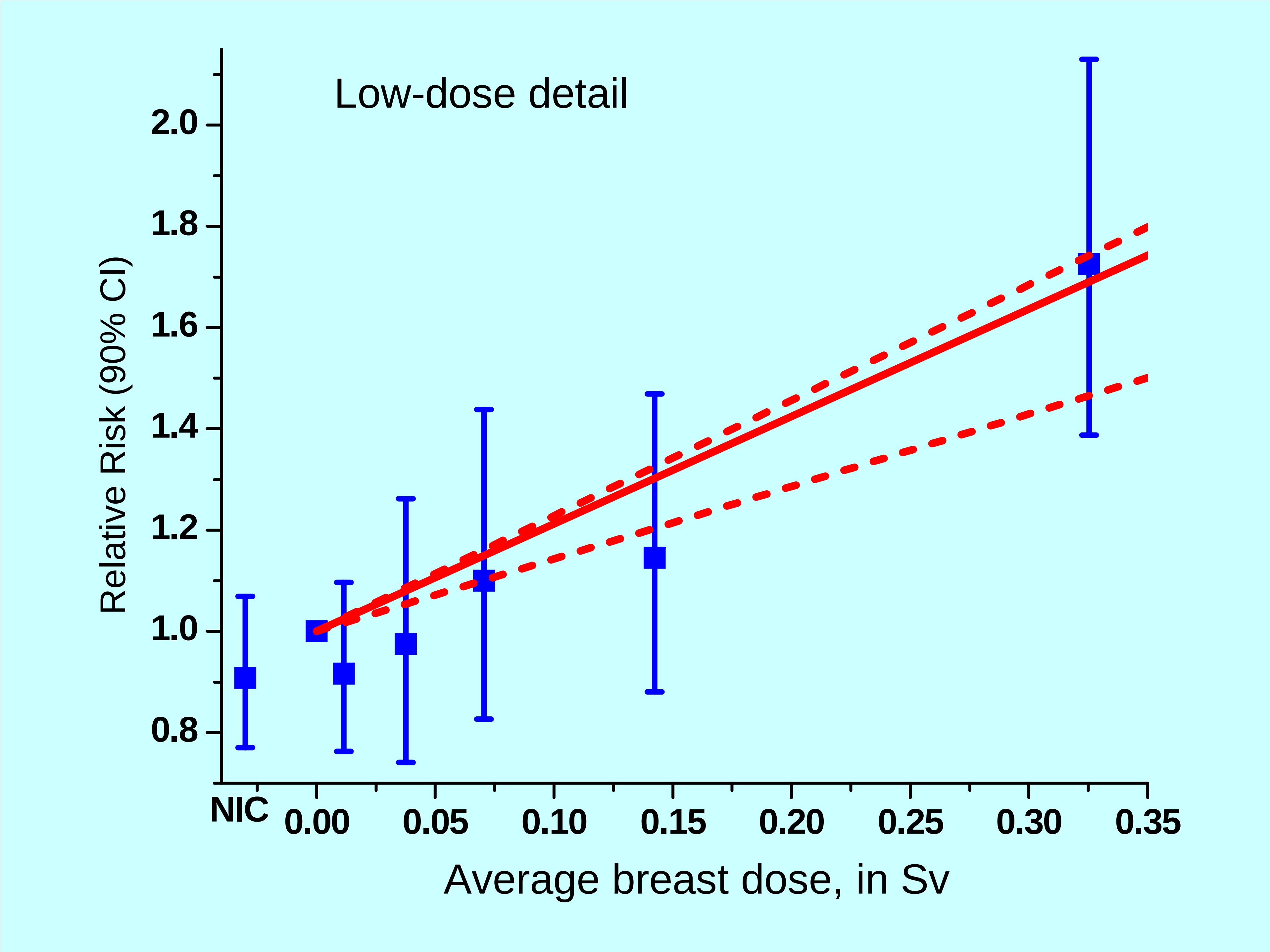
Breast Cancer Cases, 1950-1990

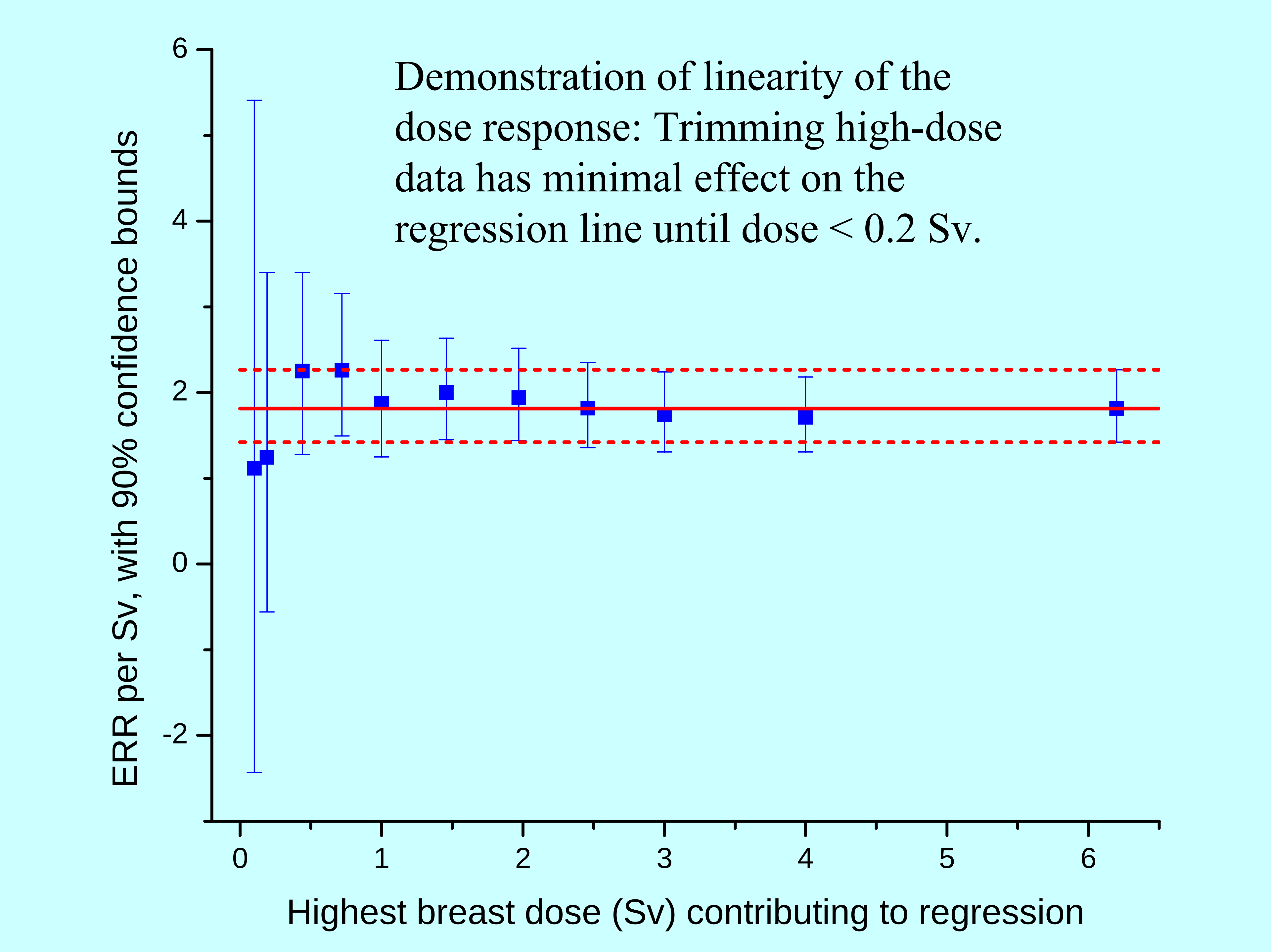
Radiation Research 2003; 160:707-17

- 1059 total cases among 70,000 women
  - 190 among non-exposed comparison subjects
  - 93 among exposed, with unknown dose
  - 876 among exposed with radiation dose estimates
  - 34 cases developed 2nd breast cancer



Dose-specific RR, and fitted linear dose response
Dose-specific relative risk, with 90% confidence limits
16
12
10
8
6
4
2
0
Unk.
dose
NIC
0
1
2
3
4
5
Case-weighted breast tissue dose, in Sv


Low-dose detail
Relative Risk (90% CI)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
NIC
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
Average breast dose, in Sv



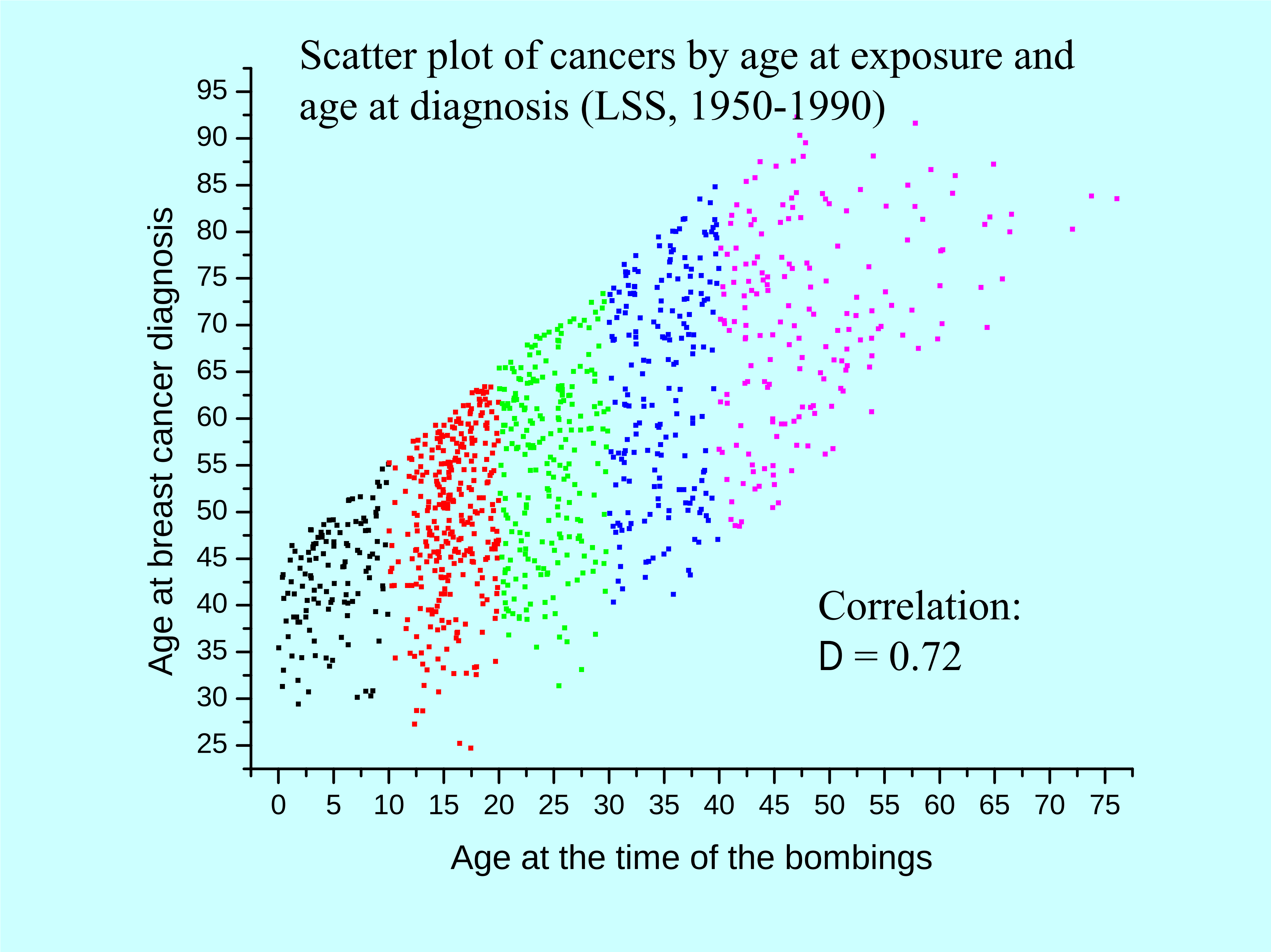
Demonstration of linearity of the dose response: Trimming high-dose data has minimal effect on the regression line until dose < 0.2 Sv.
ERR per Sv, with 90% confidence bounds
Highest breast dose (Sv) contributing to regression
6
4
2
0
-2
0
1
2
3
4
5
6

Age modification of dose-response

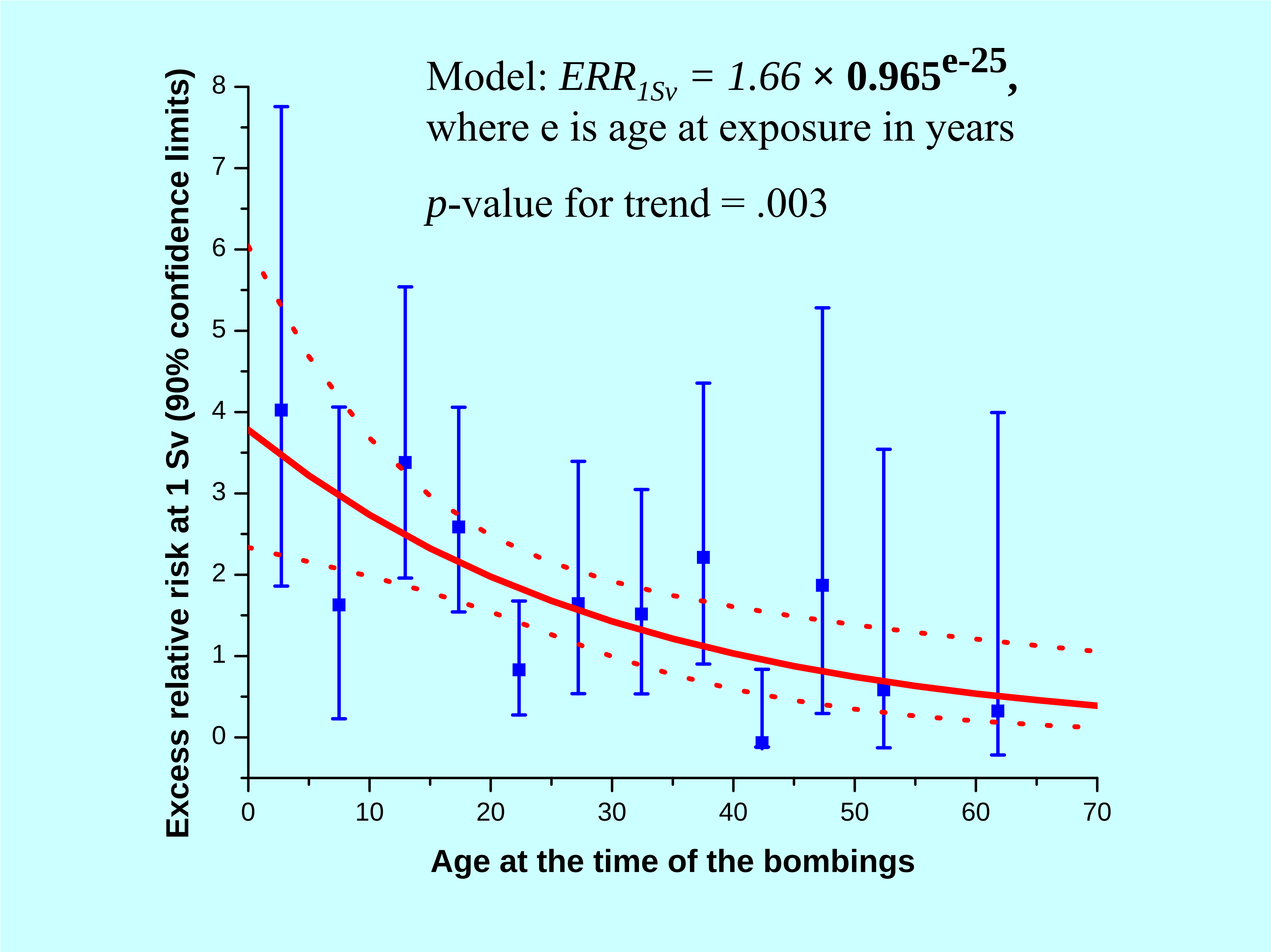
- Although not uniform, ERR in different populations tends to decline with increasing exposure age, and with age at observation for risk (attained age)
- In most studies, exposure age and attained age are correlated
  - Modifying effects are difficult to separate
- Interpretation has implications for lifetime risk and risk management

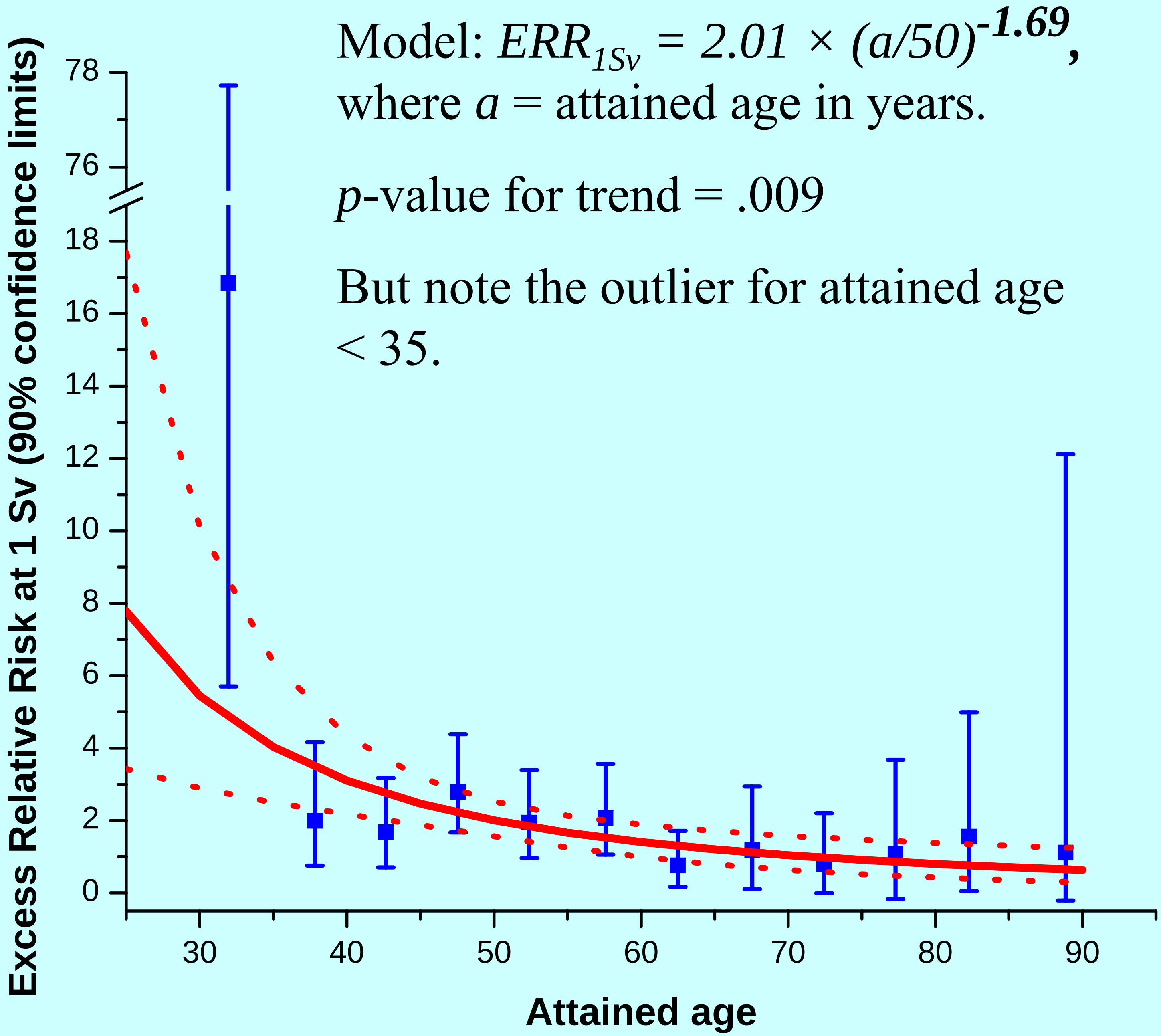
A-bomb survivors, 1950-90

- Age at diagnosis ranges from 24 to 98
- Following slide shows distribution of cases by age at exposure and age at diagnosis
  - Correlation is 72%



Scatter plot of cancers by age at exposure and age at diagnosis (LSS, 1950-1990)
Age at breast cancer diagnosis
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
Age at the time of the bombings
Correlation:
D = 0.72


Model: $ERR_{1Sv} = 1.66 \times \mathbf{0.965^{e-25}}$,
where e is age at exposure in years
p-value for trend = .003
Excess relative risk at 1 Sv (90% confidence limits)
Age at the time of the bombings
0
1
2
3
4
5
6
7
8
0
10
20
30
40
50
60
70


Model: $ERR_{1Sv} = 2.01 \times (a/50)^{\mathbf{-1.69}}$,
where a = attained age in years.
p-value for trend = .009
But note the outlier for attained age < 35.
Excess Relative Risk at 1 Sv (90% confidence limits)
78
76
18
16
14
12
10
8
6
4
2
0
30
40
50
60
70
80
90
Attained age

Analysis modified by exposure age *e* and attained age *a*

- Model:

ERR/Sv = " H exp{$ H(*e-25*) + (H (*a/50*)}

Where $ = 0.97 (p = .11)

(= 0.78 (p = .38)

But p = .009 for the two parameters combined.

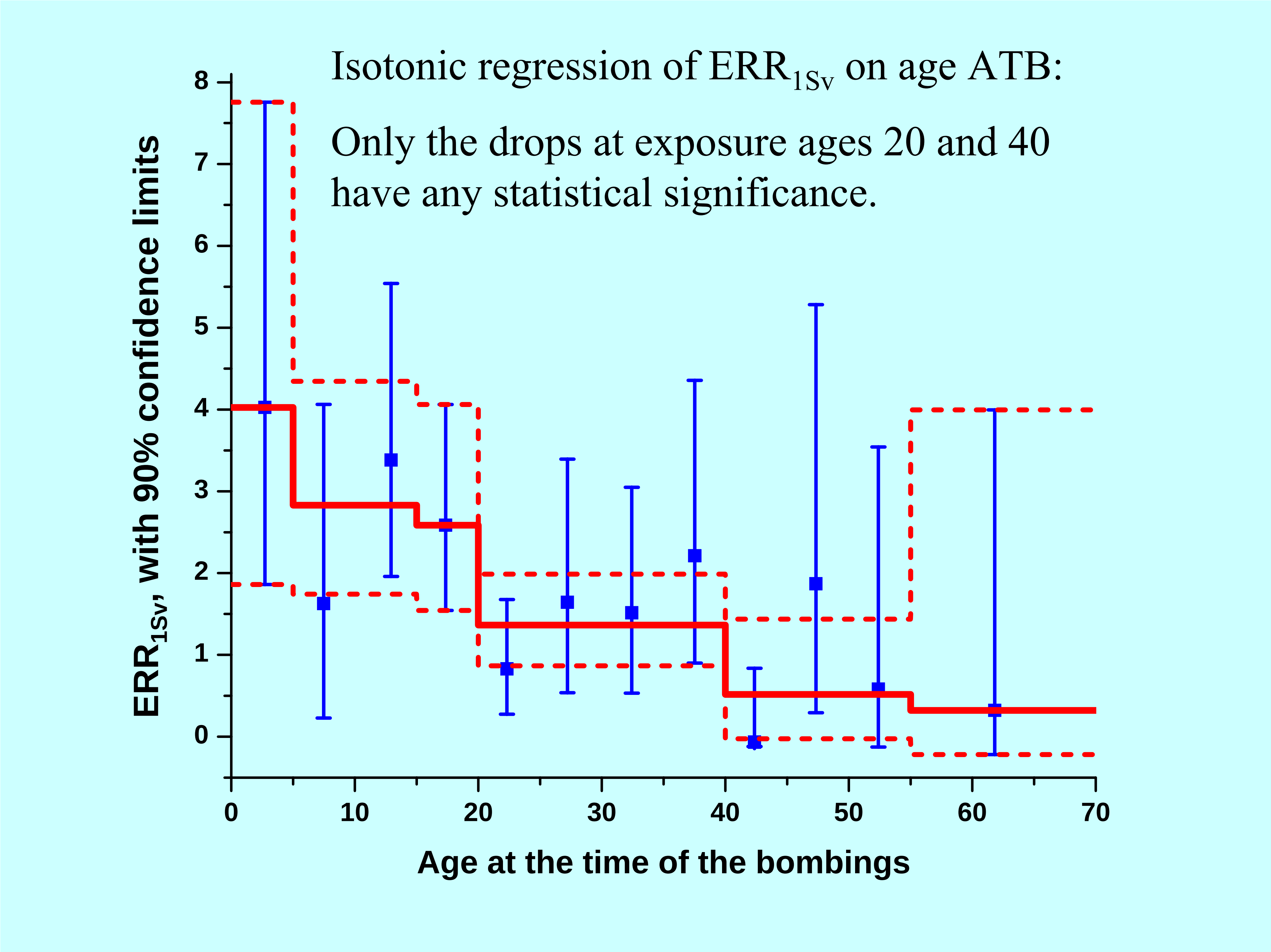
Modification of Radiation Dose Response by Age Factors

- The very high dose-related relative risk for early-onset breast cancer (at ages < 35) is clearly an anomaly.
  - Possible existence of a sensitive population subset?
  - To what extent does it drive the attained age curve?

- The high correlation of the 2 age variables ($\rho = 0.72$) makes it difficult to separate their effects.
  - Neither variable is statistically significant when both are in the exponential modification model.
  - *p = .009* for both age factors together (2 df)
  - *p = .11* for exposure age given attained age,
  - *P = .38* for attained age given exposure age

Isotonic Regression:
An Alternative Approach

- Unlike the exponential modeling of ERR_{1Sv} as a function of age ATB and attained age, isotonic regression requires only that the dependence be monotone increasing or decreasing.
- This relative lack of structure allows the data to “tell us what is going on”, at the cost of some decrease in statistical stability.

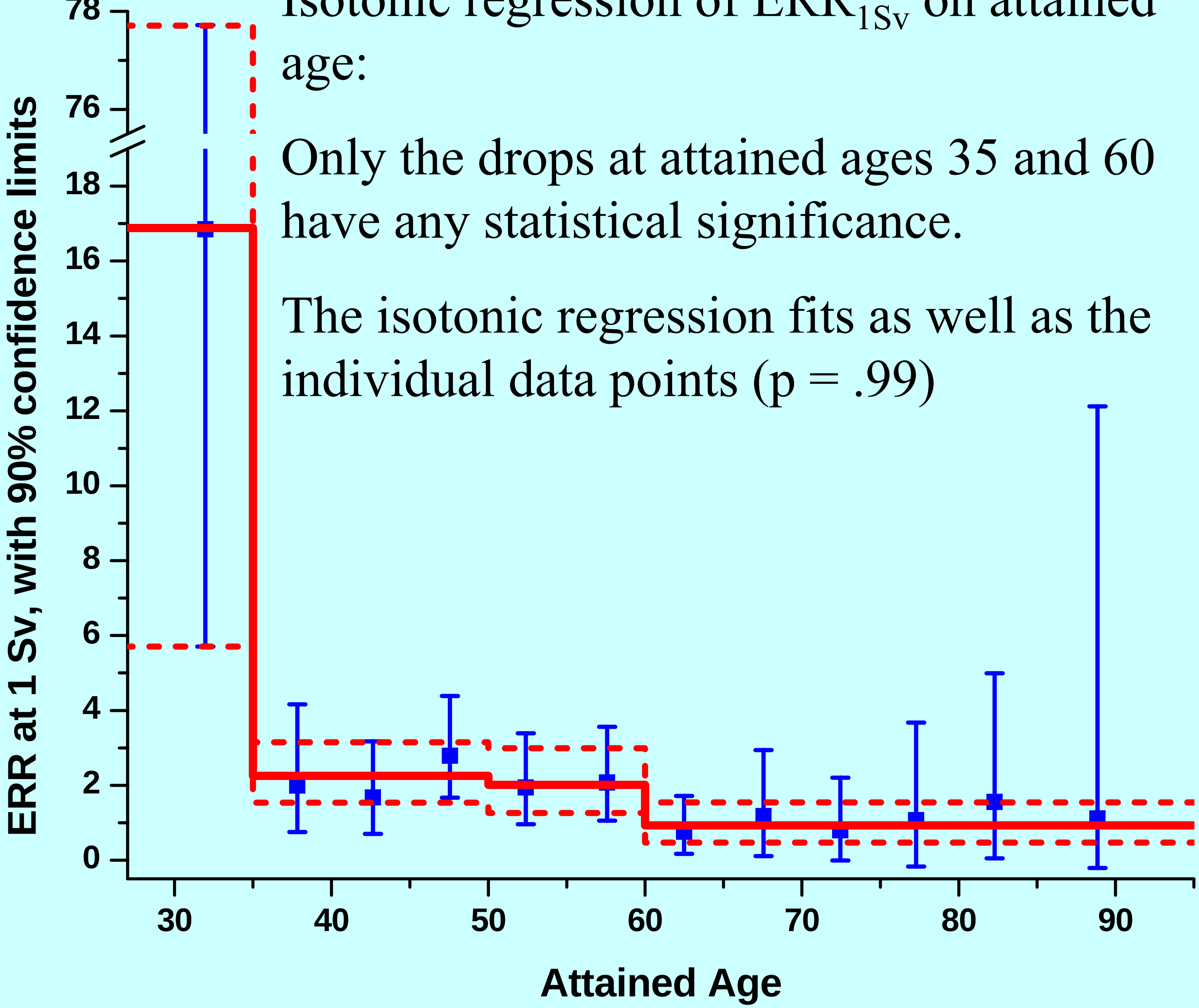


Isotonic regression of ERR1Sv on age ATB:
Only the drops at exposure ages 20 and 40
have any statistical significance.
ERR1Sv, with 90% confidence limits
8
7
6
5
4
3
2
1
0
0
10
20
30
40
50
60
70
Age at the time of the bombings

Isotonic regression of ERR_{1Sv} on attained age:

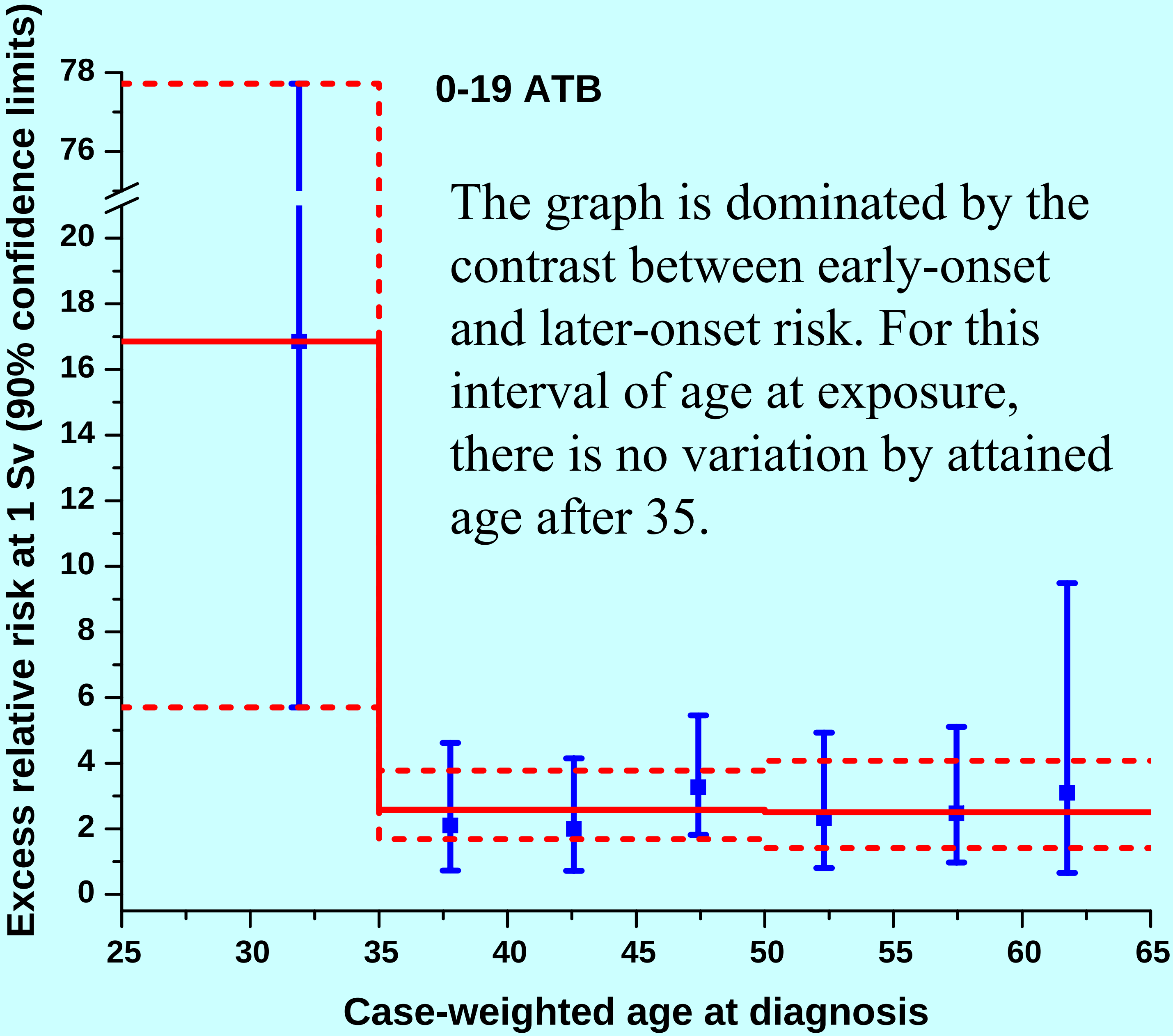
Only the drops at attained ages 35 and 60 have any statistical significance.

The isotonic regression fits as well as the individual data points (p = .99)

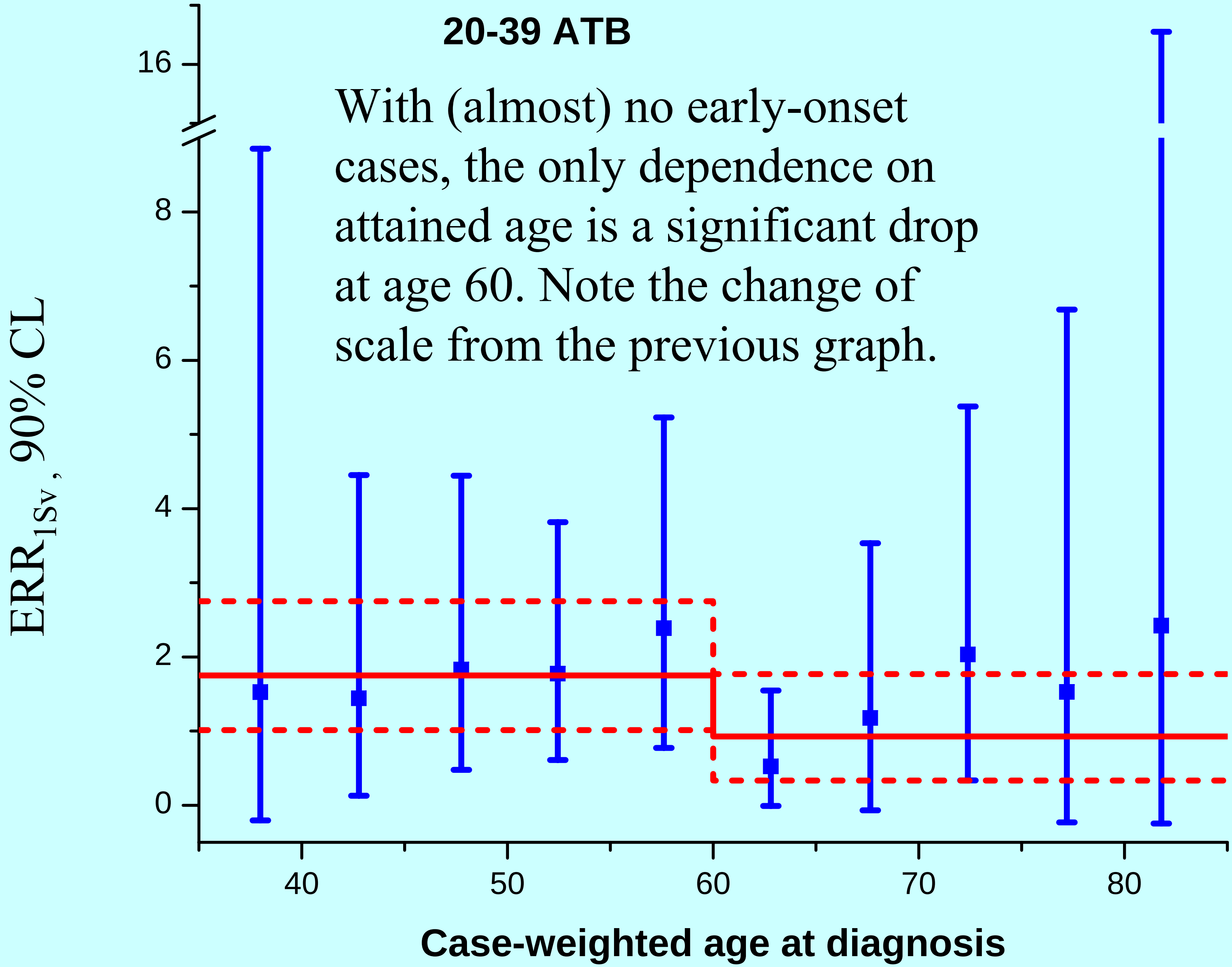


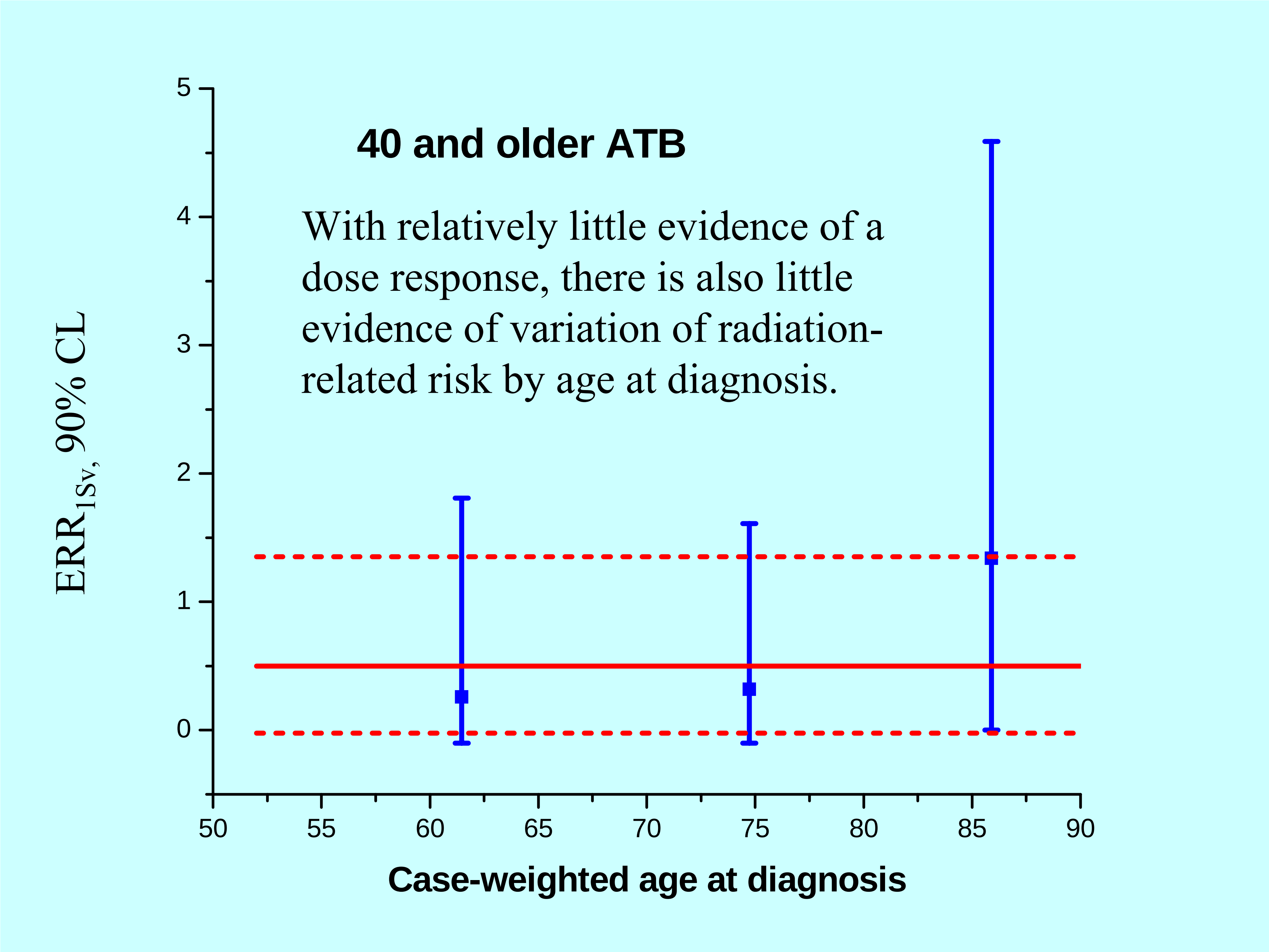
Implications of Isotonic Regression Analysis

- By age at exposure, age-specific estimates of ERR_{1Sv} are similar within 3 age intervals:
  - 0-19 ATB, 20-39 ATB, and 40+ ATB
- By attained age, there are also 3 intervals of similarity:
  - <35 (early-onset), 35-60, and 60+
- The following 3 graphs show regressions on attained age within intervals of age ATB

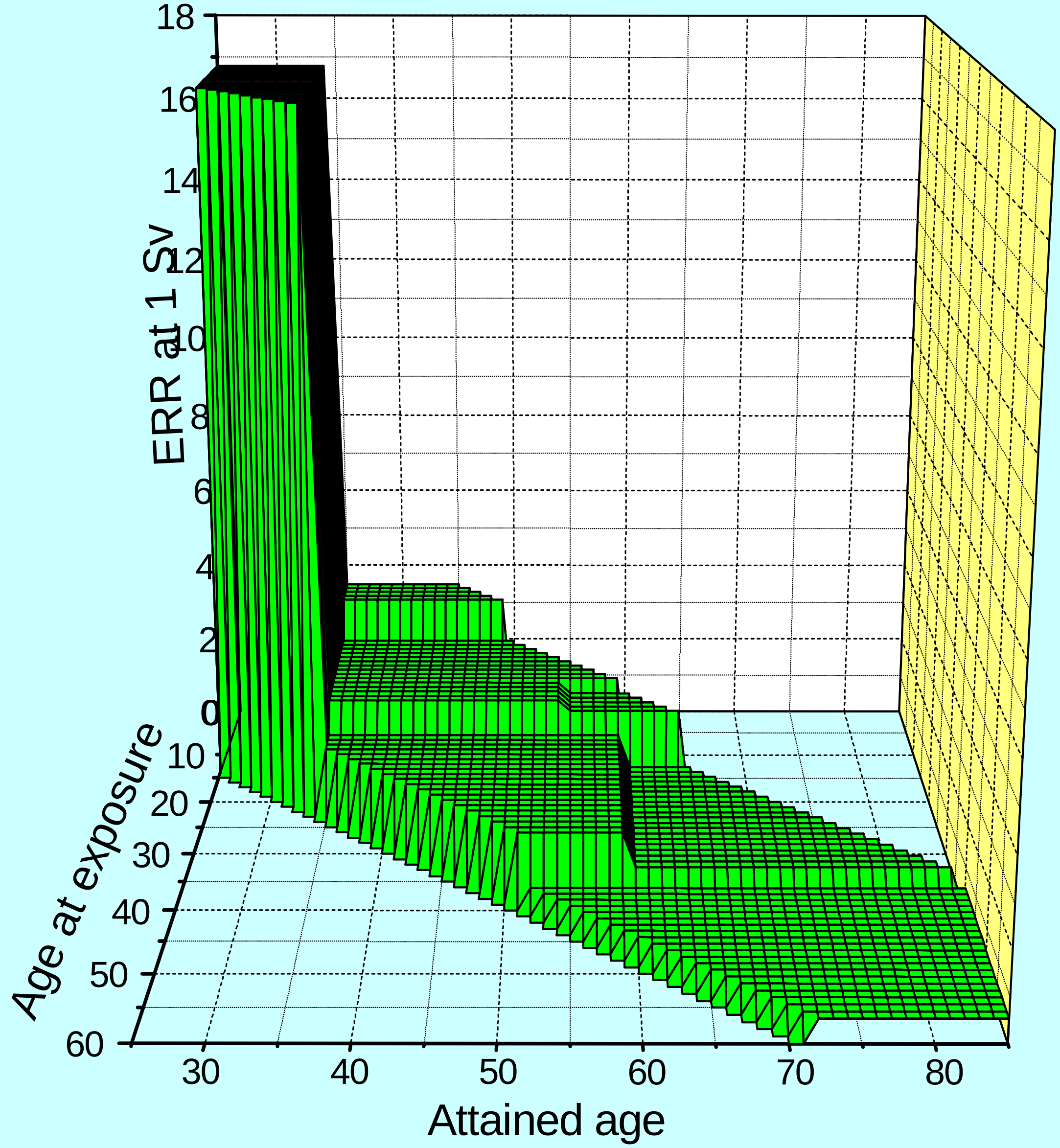


The graph is dominated by the contrast between early-onset and later-onset risk. For this interval of age at exposure, there is no variation by attained age after 35.


20-39 ATB
With (almost) no early-onset cases, the only dependence on attained age is a significant drop at age 60. Note the change of scale from the previous graph.
ERR1Sv, 90% CL
Case-weighted age at diagnosis
16
8
6
4
2
0
40
50
60
70
80


40 and older ATB
With relatively little evidence of a dose response, there is also little evidence of variation of radiation-related risk by age at diagnosis.
ERR1Sv, 90% CL
5
4
3
2
1
0
50
55
60
65
70
75
80
85
90
Case-weighted age at diagnosis

3-D plot: isotonic regression of ERR_{1Sv} on both age factors



Some Conclusions

- The “early-onset” phenomenon may be real
- Similar finding in female Hodgkin’s disease patients treated by radiation at ages <20 (van Leeuwen et al, J Clin Oncol 2000; 18:487-97)
  - ERR = 61.5 (25-127) for diagnosis under 40
  - ERR = 5.4 (0.7-20) for diagnosis age 40-49
- Genetic subgroup of high sensitivity?

Some Conclusions

- Both exposure age and age at diagnosis are important modifiers of radiation-related breast cancer risk
  - Simpler models (i.e., with only one age modifier) tend to overestimate or underestimate lifetime risk
- Higher risk for exposure before age 20
- No evidence for a “window” of higher sensitivity within that age interval, related to menarche or breast budding
  - Precursor cells are at risk (see also patients exposed in infancy for “enlarged thymus”, hemangioma)

Modified exponential model:

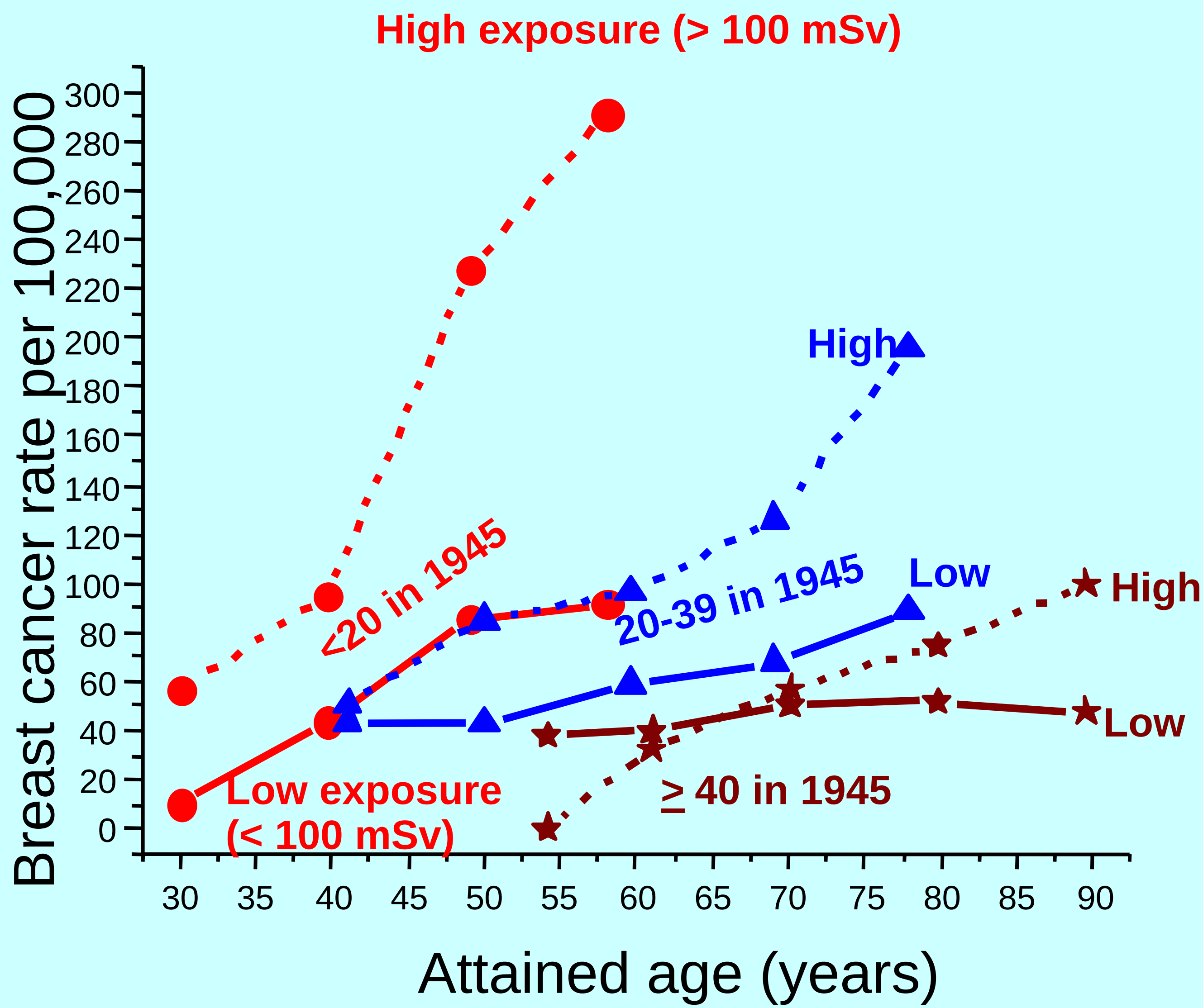
$$\mathrm{ERR/Sv} = \text{"}\ \mathrm{H}\ \mathrm{exp}\{{*}\mathrm{HI}_{35}(a) + \$\mathrm{H}(e\text{-}25) + (\mathrm{Hln}(a/50))\}$$

- ERR at 1 Sv proportional to dose
  - times an indicator for early-onset cancer (*p=.008 for **)
  - times an exponential in exposure age *(p= .041 for $)*
  - exponential in attained age not significant *(p>.5 for ()*

- Exposure age and early-onset cancer more important than variation by attained age after 35

- *Note: different case-inclusion rules lead to somewhat weaker conclusions about the separate roles of exposure age and attained age.*

Both baseline breast cancer rates and radiation-related excess vary by birth cohort



Speculation

- Some of the variation in ERR_{1Sv} by exposure age may reflect normal life events
- Full-term pregnancies, ~ age 20?
  - Differentiated breast cells less sensitive to chemical carcinogenesis (Russo)
- Approach of menopause, ~ age 40 in 1945?
  - Possible interaction of radiation exposure with serum estrogen levels?

Explanations for age ATB effect?

- Case-control interview study of potential modifiers of radiation-related risk (Cancer Causes Control 1994;5:157-65, 167-76).
  - Cases and controls matched on radiation dose
- Major risk factors (all were protective):
  - Young age 1st full-term pregnancy
  - multiple births
  - lengthy cumulative lactation period

Explanations (continued)

- Interactions with radiation dose were
  - Consistent with multiplicative model
  - Inconsistent with additive model
- i.e., all were protective against radiation-related breast cancer risk
- Moreover, this was especially true for women exposed before age 16.
  - reproductive history after exposure, as well as before, modified radiation-related risk
  - Terminal end bud differentiation of breast cells is protective against effects of prior exposure to experimental carcinogens (Clifton & Crowley, Ca Res 1978; 38: 1507-13)

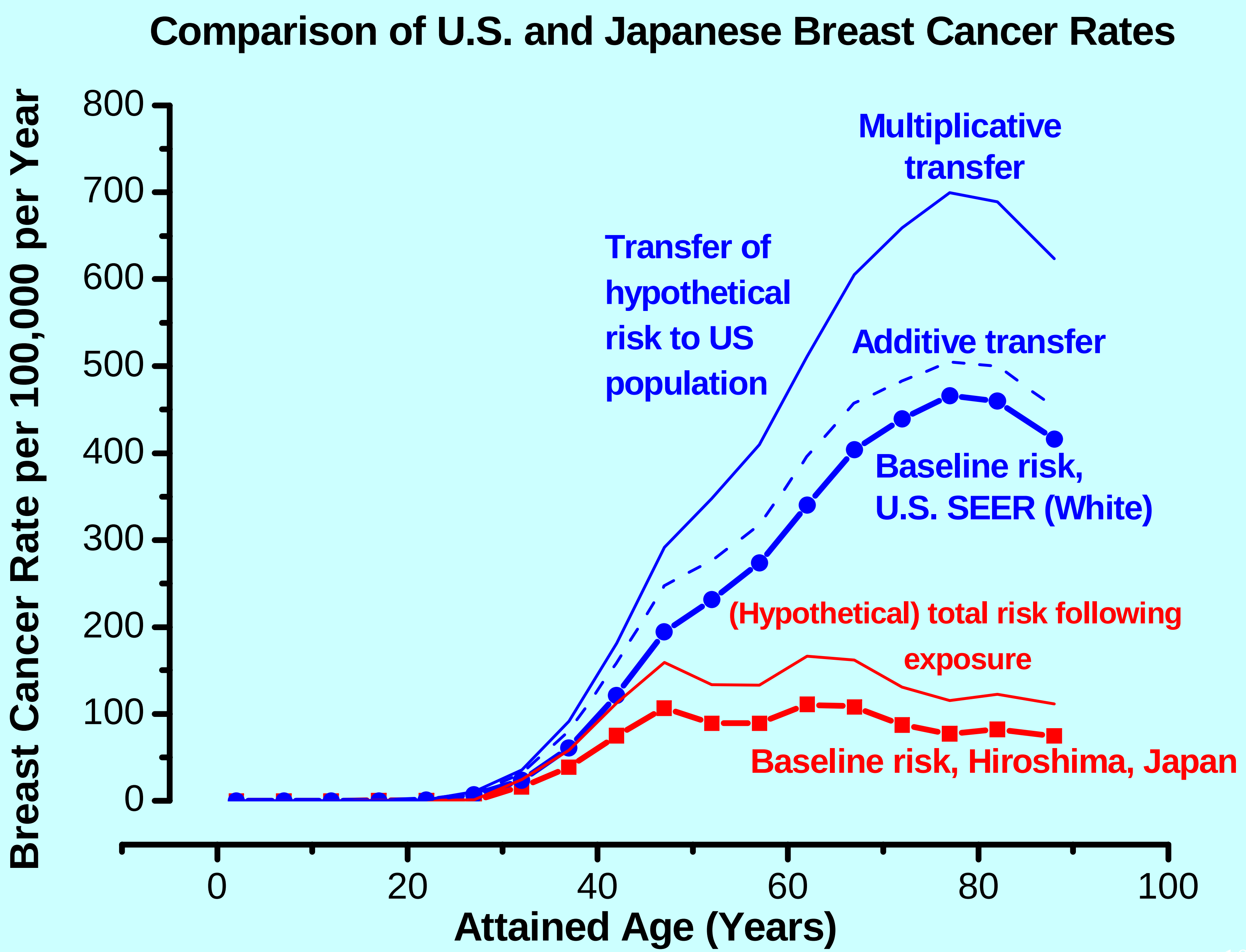
Speculation

- Secular changes (increases) in Japanese breast cancer rates -- and radiation-related risks -- may (in part) reflect post-WWII changes in Japanese reproductive patterns
- Case-control interview study:

	<20 ATB	20+ ATB
Av. age 1st full-term preg	24.8	23.8
Av. number of deliveries	2.0	3.1
Av. cum. lactation (yrs)	1.3	2.5

An unavoidable problem

- Breast cancer rates are ~ 4 times higher in the US than in Japan
- Rates among granddaughters of Japanese immigrants to the US are typical of the US population
- Presumably, life-style factors are involved
- How do they interact with radiation dose?
- How do we apply the LSS information to a US population?


Comparison of U.S. and Japanese Breast Cancer Rates
Breast Cancer Rate per 100,000 per Year
800
700
600
500
400
300
200
100
0
0
20
40
60
80
100
Attained Age (Years)
Multiplicative transfer
Transfer of hypothetical risk to US population
Additive transfer
Baseline risk, U.S. SEER (White)
(Hypothetical) total risk following exposure
Baseline risk, Hiroshima, Japan

Epidemiological comparisons

- Dose-response estimates can be compared among irradiated populations with varying baseline breast cancer rates
  - Best effort to date is pooled analysis of 8 cohorts (Preston et al, Rad. Res. 2002)
- Uncertain RBE of medical x ray cf. gamma ray is a confounding factor
  - RBE > 1 would increase dose-specific RR for medical cf. A-bomb survivors
  - Conventional wisdom: RBE ~ 2
- Fractionation effect is another confounding factor
  - ICRP: DDREF = 2 (but generally agreed to be uncertain)

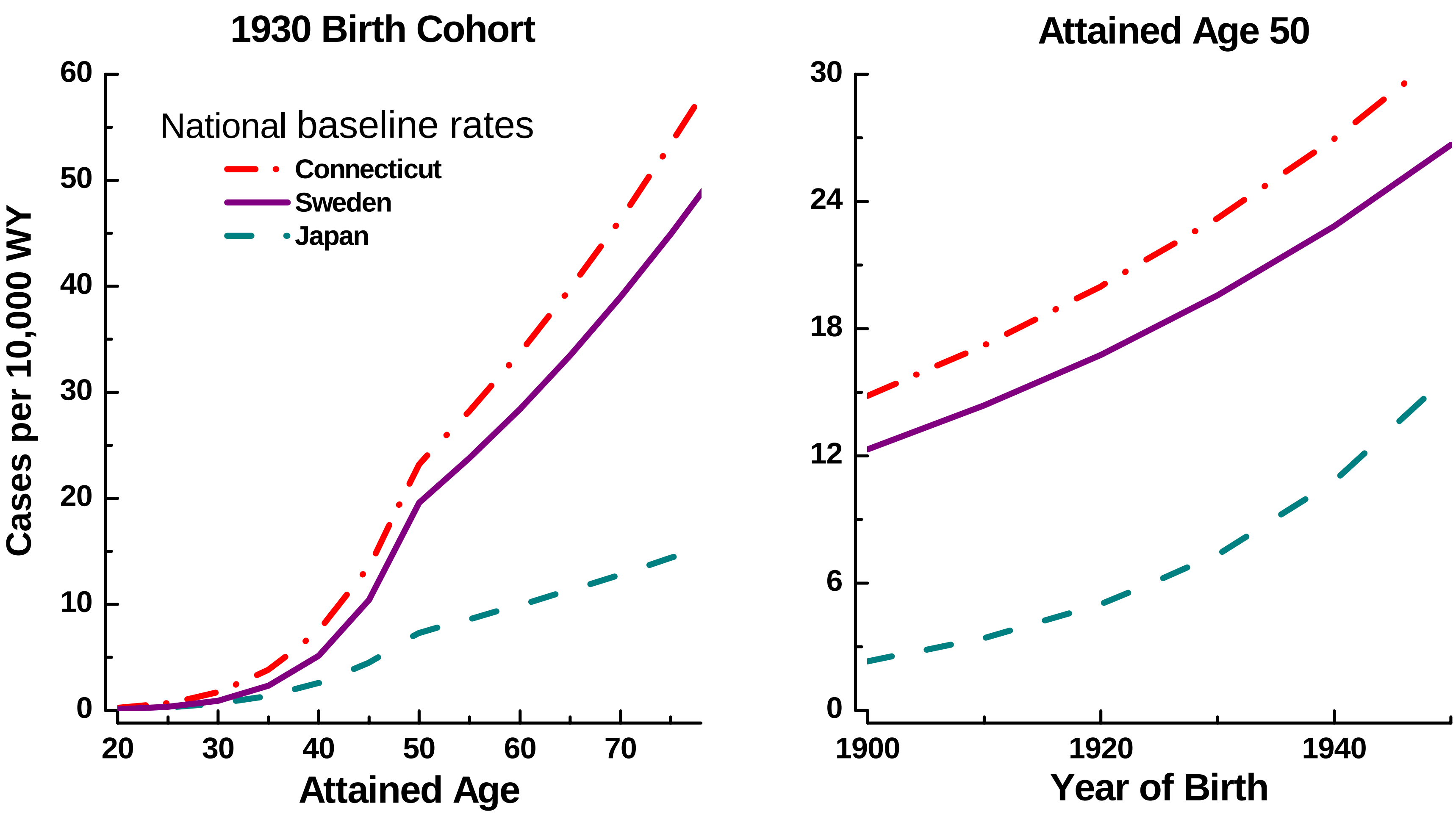
Populations studied by Preston

- A-bomb survivors , Tumor Reg. 1958-87 (LSS)
- Massachusetts TB fluoroscopy patients
  - Original (TBO)
  - Extension (TBX)
- New York mastitis patients (APM)
- Rochester infants with “enlarged thymus” (THY)
- Sweden benign breast disease patients (BBD)
- Sweden hemangioma patients
  - Gothenburg (HMG)
  - Stockholm (HMS)

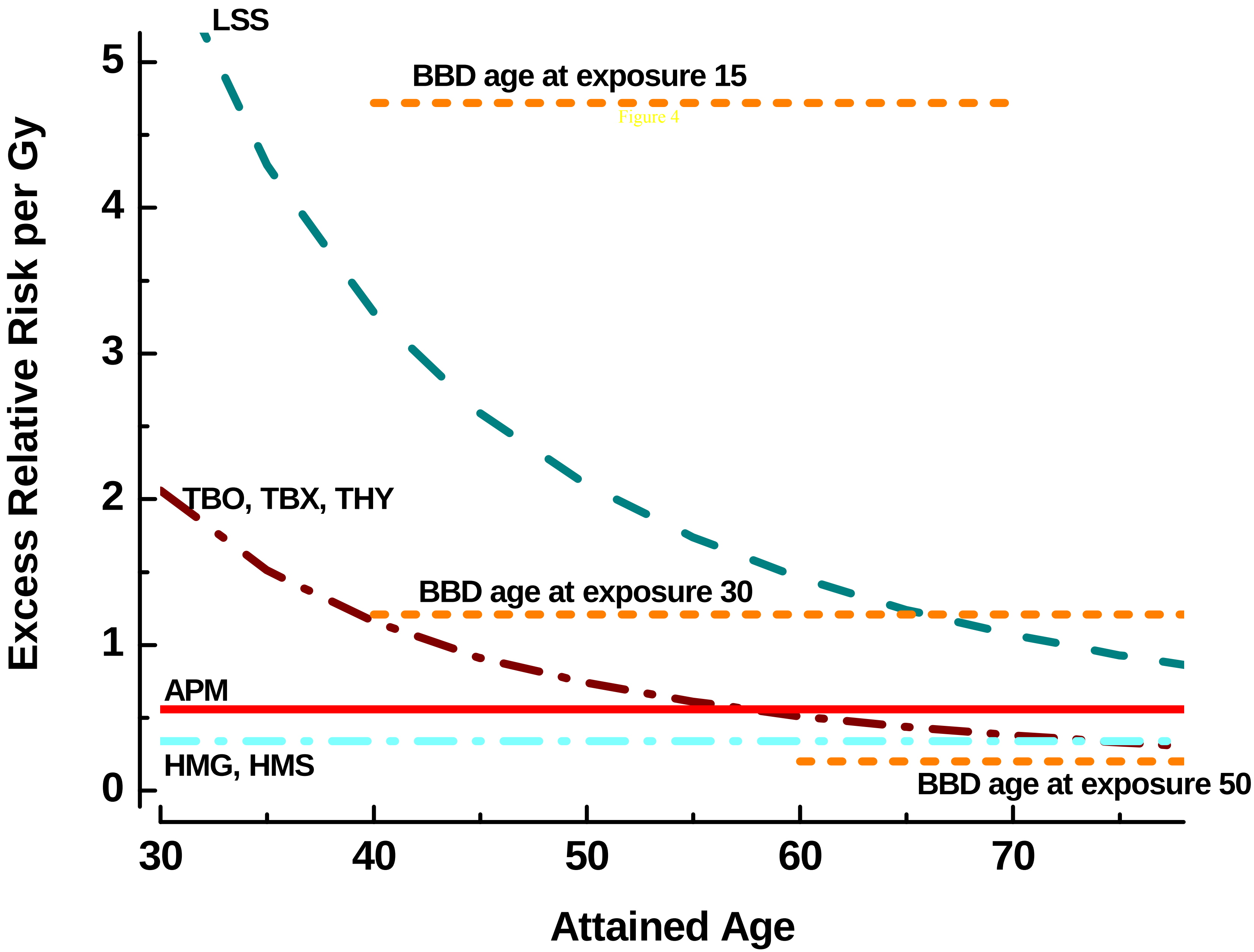
Population properties

- LSS: 707 cases, mean dose 0.3 Sv (0-5)
- TBO, TBX: 103 & 108 cases, many low-dose x-ray fractions, high dose rates, 0-5 Gy
- APM: 114 cases, few fractions, 3.8 (0.6-14)
- THY: 34 cases, few fractions, 0.7 (0.02-7.5)
- BBD: 210 cases, few fractions, 5.8 (0.02-50)
- HMG, HMS: 75 & 155 cases, protracted, low-dose fractions, 0.17 (0-22), 0.5 (0-35)

Figure 1

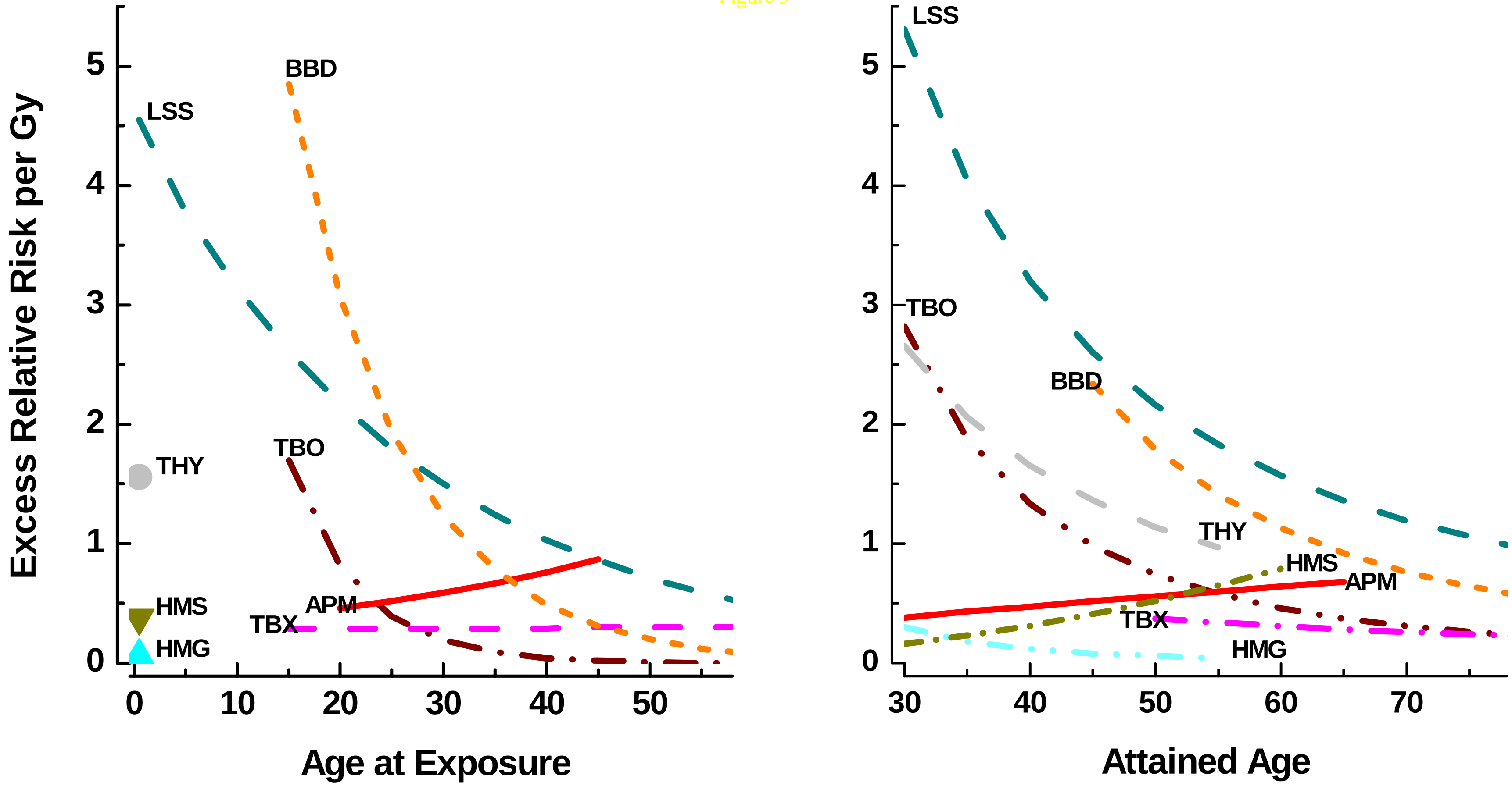


1930 Birth Cohort
National baseline rates
Connecticut
Sweden
Japan
Cases per 10,000 WY
0
10
20
30
40
50
60
20
30
40
50
60
70
Attained Age
Attained Age 50
0
6
12
18
24
30
1900
1920
1940
Year of Birth


LSS
BBD age at exposure 15
Figure 4
TBO, TBX, THY
BBD age at exposure 30
APM
HMG, HMS
BBD age at exposure 50
Excess Relative Risk per Gy
Attained Age
0
1
2
3
4
5
30
40
50
60
70

ERR per Gy, by age at exposure (left) and attained age (right) Preston et al, 2002

Figure 3



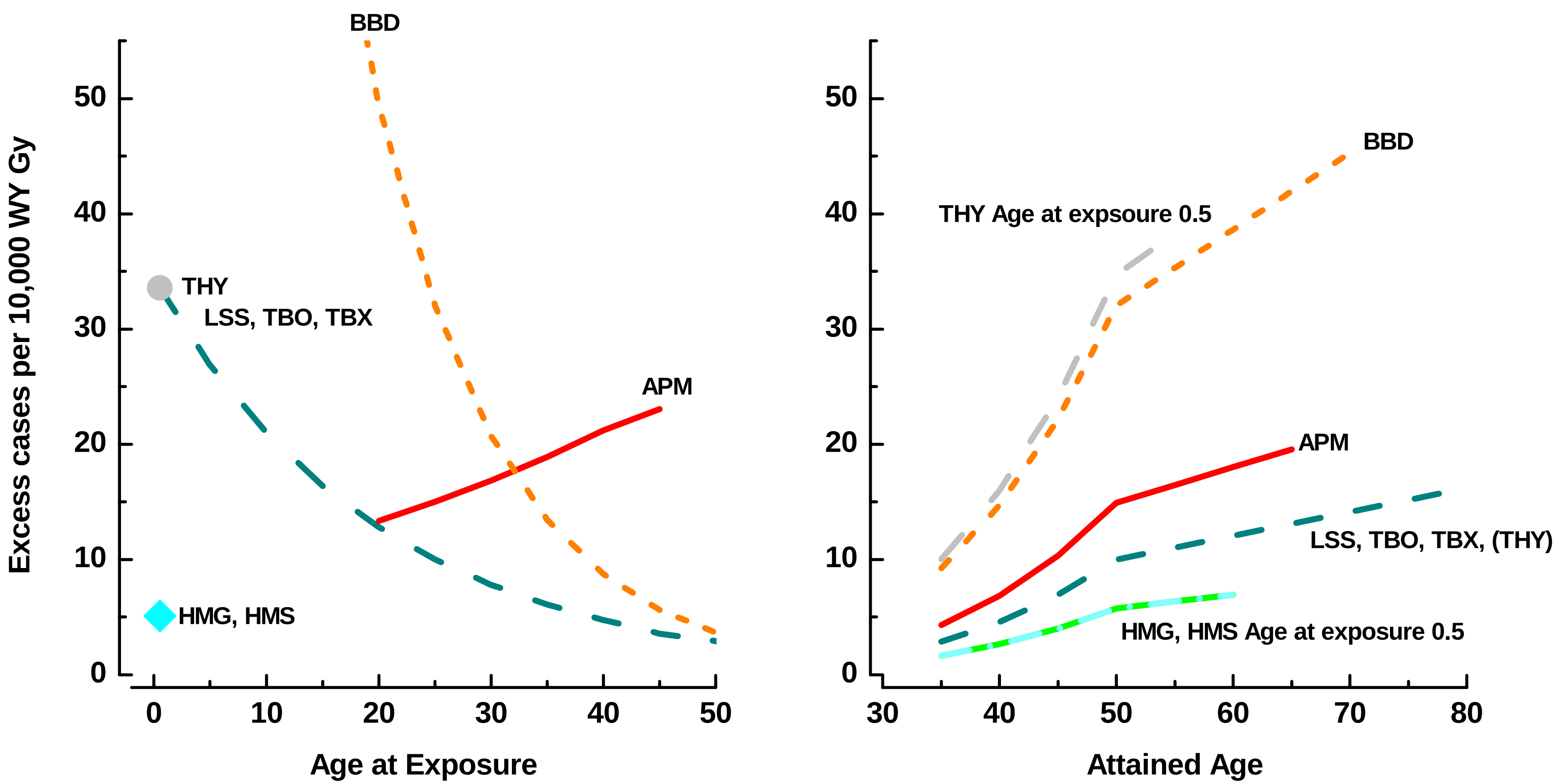

Excess cases per 10,000 WY Gy
BBD
THY
LSS, TBO, TBX
APM
HMG, HMS
Age at Exposure
THY Age at expsoure 0.5
BBD
APM
LSS, TBO, TBX, (THY)
HMG, HMS Age at exposure 0.5
Attained Age
0
10
20
30
40
50
30
40
50
60
70
80

Figure 6

Conclusions re transfer

- Dose-specific excess relative risk significantly greater in A-bomb survivor population than in western, medically-irradiated populations
- Dose-specific excess absolute risks similar among populations
- Not a uniform result, some uncertainty
- Preston et al, Radiation Research, 2002

Unresolved Issues

- Does the early-onset risk anomaly reflect presence of a sensitive genetic subpopulation, & if so, what are its characteristics?
- What is the projected lifetime risk of women exposed at young ages?
- Is breast cancer really different from other cancers re modification by age?

Acknowledgements

- This work is a collaboration with the Radiation Effects Research Foundation in Hiroshima and Nagasaki
- Collaborators:
  - Masayoshi Tokunaga, MD
  - Kojiro Koyama, MD
  - Midori Soda, PhD
  - Dale Preston, PhD
  - Issei Nishimori, MD
  - Shoji Tokuoka, MD